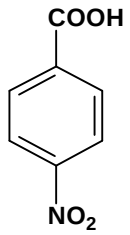
BIOASSAY REPORT SUMMARY



p-Nitrobenzoic Acid 62-23-7 C61778B

NTP-TR-442 (1994) Southern Research Institute

nitro aromatic acid

Organic synthesis and an intermediate in the manufacture of pesticides, dyes, and industrial solvents

E.I. du Pont de Nemours >99% pure

F344/N Rats ♂	0; 1,250; 2,500; or 5,000 ppm for 103 weeks	Feed	♀	0; 1,250; 2,500; or 5,000 ppm for 103 weeks	Feed

NEGATIVE

Preputial Gland: Carcinoma: 1/50, 1/50, 4/49, 6/50; Life Table, P(C)=0.031; Logistic Regression, P(C)=0.002, P(HD)=0.009; CA, P(C)=0.013

Adenoma or Carcinoma: 4/50, 4/50, 8/49, 9/50; Logistic Regression, P(C)=0.024

Skin (Subcutaneous Tissue): Fibrosarcoma: 1/50, 0/50, 0/50, 4/50; Logistic Regression, P(C)=0.036; CA, P(C)=0.028

Pancreas: Adenoma: 2/49, 3/50, 0/49, 0/50; Life Table, P(C)=0.032N; Logistic Regression, P(C)=0.040N

Pancreatic Islets: Adenoma or Carcinoma: 3/49, 1/50, 2/49, 0/50; Life Table, P(HD)=0.048N

Pituitary Gland (Pars Distalis): Adenoma: 19/49, 12/50, 16/49, 12/49; Life Table, P(C)=0.013N, P(HD)=0.003N; Logistic Regression, P(HD)=0.020N

Testes: Adenoma: 44/50, 45/50, 44/49, 36/50; Life Table, P(C)<0.001N, P(HD)=0.001N; Logistic Regression, P(C)<0.001N, P(HD)=0.007N; CA, P(C)=0.010N; Fisher, P(HD)=0.039N

All Organs: Mononuclear Cell Leukemia: 29/50, 35/50, 26/50, 2/50; Life Table, P(C,HD)<0.001N, Logistic Regression, P(C,HD)<0.001N; CA, P(C)<0.001N; Fisher, P(HD)<0.001N

Benign Neoplasms: 48/50, 48/50, 48/50, 42/50; Life Table, P(C)=0.002N, P(HD)=0.003N; Logistic Regression, P(C)<0.001N, P(HD)=0.005N; CA, P(C)=0.010N; Fisher, P(HD)=0.046N

POSITIVE

Neoplastic Lesions

Clitoral Gland: Adenoma: 4/50, 12/49, 10/49, 12/50; Life Table, P(C)=0.034, P(LD,HD)=0.013, P(MD)=0.030; Logistic Regression, P(C)=0.046, P(LD)=0.013, P(MD)=0.050, P(HD)=0.023; Fisher, P(LD)=0.024, P(HD)=0.027

Adenoma or Carcinoma: 4/50, 14/49, 15/49, 15/50; Life Table, P(C)=0.008, P(LD)=0.005, P(MD)=0.001, P(HD)=0.002; Logistic Regression, P(C)=0.011, P(LD,HD)=0.004, P(MD)=0.003; CA, P(C)=0.018; Fisher, P(LD)=0.008, P(MD)=0.004, P(HD)=0.005

Pituitary Gland (Pars Distalis): Adenoma: 18/50, 27/50, 25/50, 23/49; Life Table, P(LD)=0.030, P(MD)=0.023; Logistic Regression, P(LD)=0.034, P(MD)=0.025

Adenoma or Carcinoma: 19/50, 27/50, 25/50, 23/49; Life Table, P(LD)=0.045, P(MD)=0.035; Logistic Regression, P(MD)=0.038

Uterus: Stromal Polyp: 5/50, 11/50, 12/50, 5/50; Life Table, P(LD)=0.050, P(MD)=0.023

Stromal Polyp or Stromal Sarcoma: 5/50, 12/50, 13/50, 5/50; Life Table, P(LD)=0.032, P(MD)=0.014; Logistic Regression, P(LD)=0.047, P(MD)=0.044; Fisher, P(MD)=0.033

All Organs: Benign Neoplasm: 40/50, 41/50, 44/50, 41/50; Life Table, P(MD)=0.035

Benign or Malignant Neoplasms: 44/50, 48/50, 50/50, 45/50; Life Table, P(MD)=0.017; Logistic Regression, P(MD)=0.032; Fisher, P(MD)=0.013

Thyroid Gland (C-Cell): Adenoma: 9/50, 5/49, 4/50, 2/50; Life Table, P(C)=0.045N; Logistic Regression, P(C)=0.023N, P(HD)=0.027N; CA,

p-Nitrobenzoic Acid

Malignant Neoplasms: 39/50, 38/50, 35/50, 19/50; Life Table, P(C,HD)<0.001N; Logistic Regression, P(C,HD)<0.001N; CA, P(C)<0.001N; Fisher, P(HD)<0.001N Benign or Malignant Neoplasms: 49/50, 50/50, 49/50, 46/50; Life Table, P(C)=0.005N, P(HD)=0.009N; Logistic Regression, P(C)=0.002N, P(HD)=0.026N; CA, P(C)=0.034N	P(C)=0.019N, Fisher, P(HD)=0.026N Adenoma or Carcinoma: 10/50, 5/49, 6/50, 2/50; Life Table, P(C)=0.041N, P(HD)=0.038N; Logistic Regression, P(C)=0.021N, P(HD)=0.016N, CA, P(C)=0.016N; Fisher, P(HD)=0.014N All Organs: Mononuclear Cell Leukemia: 17/50, 11/50, 3/50, 0/50; Life Table, P(C,HD)<0.001N, P(MD)=0.008N; Logistic Regression, P(C,MD,HD)<0.001N; CA, P(C)<0.001N; Fisher, P(MD,HD)<0.001N Malignant Neoplasms: 22/50, 19/50, 22/50, 11/50; Logistic Regression, P(C)=0.007N, P(HD)=0.004N; CA, P(C)=0.017N; Fisher, P(HD)=0.016N

Nonneoplastic Lesions

None	Mild hematologic toxicity

B6C3F$_1$ Mice ♂	0; 1,250; 2,500; or 5,000 ppm for 103 weeks	Feed	♀	0; 1,250; 2,500; or 5,000 ppm for 103 weeks	Feed
NEGATIVE			NEGATIVE		

Neoplastic Lesions

Liver: Hepatocellular Carcinoma: 8/50, 13/50, 16/50, 8/48; Fisher, P(MD)=0.050 Small Intestine (Jejunum): Carcinoma: 3/50, 1/50, 0/50, 0/50; Life Table, P(C)=0.039N; Logistic Regression, P(C)=0.042N; CA, P(C)=0.044N All Organs: Hemangiosarcoma: 6/50, 2/50, 2/50, 1/50; Life Table, P(C)=0.032N, P(HD)=0.044N; Logistic Regression, P(C)=0.040N, P(HD)=0.049N; CA, P(C)=0.042N Hemangioma or Hemangiosarcoma: 6/50, 3/50, 2/50, 1/50; Life Table: P(C)=0.028N, P(HD)=0.044N; Logistic Regression, P(C)=0.035N, P(HD)=0.049N; CA, P(C)=0.035N	Lung: Alveolar/Bronchiolar Adenoma: 3/50, 5/49, 3/50, 8/50; Life Table, P(C)=0.035, P(HD)=0.050 Alveolar/Bronchiolar Carcinoma: 0/50, 5/49, 1/50, 1/50; Life Table, P(LD)=0.029; Logistic Regression, P(LD)=0.029; Fisher, P(LD)=0.027 Alveolar/Bronchiolar Adenoma or Carcinoma: 3/50, 10/49, 4/50, 9/50; Life Table, P(LD)=0.031, P(HD)=0.027; Logistic Regression, P(LD)=0.031, P(HD)=0.039; Fisher, P(LD)=0.033 Harderian Gland: Adenoma: 3/50, 1/49, 0/50, 0/50; Logistic Regression, P(C)=0.047N; CA, P(C)=0.044N

Nonneoplastic Lesions

None	None

Comments

In rats, 2-year survival rates were similar to that of the controls in the low- and mid-dose males and

marginally greater in high-dose males, partly due to a decrease in the severity of nephropathy and a decrease in the incidence in mononuclear cell leukemia. Survival of exposed females was similar to that of controls. Final mean body weights were similar to that of the controls in dosed males and lower in mid- and high-dose females. Feed consumption by exposed males and females was similar to that by controls.

The slight increase in preputial gland neoplasms in high-dose male rats was not considered to be chemical related because the life table test indicated that it was not statistically significant, the incidence fell within the historical controls range, and there was no chemical-related increase in preputial gland hyperplasia.

The increased incidences of clitoral gland neoplasms in female rats were considered to be some evidence of carcinogenic activity.

Two-year survival rates of exposed mice were similar to those of the controls. Final mean body weights of high-dose males and females were lower than those of controls. Feed consumption by exposed mice was similar to that by the controls.

There was no evidence of carcinogenic activity in male or female mice. The increased incidence of alveolar/bronchiolar adenoma or carcinoma in females were not considered to be chemical related because these neoplasms were not increased by the trend statistic, the combined incidences were within the historical control range, and there was no increase in the incidence of alveolar epithelial hyperplasia.
Exposure may occur through its use pattern as well as through exposure to other chemicals that are metabolized or hydrolyzed to *p*-nitrobenzoic acid, including *p*-nitrobenzyl chloride, *p*-nitrotoluene, and 5-(4-nitrophenyl)-2,4-pentadienal (spy dust). The National Institute for Occupational Safety and Health (NIOSH) has estimated that there are 42,700 workers potentially exposed to *p*-nitrobenzoic acid in 16 different industries.

Metabolism may occur through reduction of the nitro group to yield *p*-aminobenzoic acid as well as pathways involving conjugation of the carboxylic acid group with glycine or glucuronic acid and reduction to *p*-aminobenzoic acid, which may then be conjugated at the carboxylic acid group or acetylated at the amino substituent. Urinary metabolites in Wistar rats following an oral intraperitoneal dose were free *p*-aminobenzoic acid, conjugated *p*-aminobenzoic acid, *p*-nitrobenzoic acid, and conjugated *p*-nitrobenzoic acid.

p-Nitrobenzoic acid was positive, in the absence of S9 activation, in the *Bacillus subtilis* rec assay for growth inhibition due to DNA damage, and it induced gene mutations in *Salmonella typhimurium*, with and without S9. No induction of unscheduled DNA synthesis was noted in rat hepatocytes treated *in vitro* with up to 1,000 nmol *p*-nitrobenzoic acid/mL. Unpublished NTP data show that *p*-nitrobenzoic acid induces sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. However, no increase in the frequency of micronucleated erythrocytes was observed in the peripheral blood of male and female mice administered *p*-nitrobenzoic acid in feed for 13 weeks.

Technical Report Date: 12/94
BRS Date: 11/95